



Pharmacy

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Update

SPECIAL ISSUE

Drug Information Service
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Antiemetic Usage Guidelines at the NIH Clinical Center

The 5-HT₃ serotonin receptor antagonists (e.g., ondansetron, granisetron, and dolasetron) have proven to be highly effective agents that improve antiemetic outcome and quality of life for patients receiving chemotherapy, radiation therapy and for surgical patients at risk for post operative nausea and vomiting. However, these agents are expensive and have significantly impacted the NIH Clinical Center (CC) drug budget since 1991 when ondansetron was first added to the NIH formulary. NIH usage guidelines to ensure appropriate prescribing for ondansetron were first implemented in 1993 and later revised in 1996 after granisetron was added to the NIH formulary. In 2002, an antiemetic task force was formed and charged by the NIH Pharmacy and Therapeutics (P&T) Committee to update and revise usage guidelines for the 5-HT₃ receptor antagonists and antiemetics in general.

The NIH CC Antiemetic Task Force was assembled in April 2002 and comprised representative physicians from the NCI (Surgery, Medicine, Radiation Oncology), the NHLBI, the Department of Anesthesia & Surgical Services, and the Pain & Palliative Care Service. Additional members included clinical specialists from the departments of Pharmacy and Nursing. The revised NIH CC guidelines were completed by the task force in December, 2002 and approved by the NIH P&T Committee on January 16, 2003.

The new guidelines have incorporated the following changes: (1) Ondansetron (Zofran®) has been selected as the primary 5-HT₃ antagonist for the NIH CC. Granisetron (Kytril®) has been retained as a formulary agent but should be reserved for therapeutic failures or other unique clinical situations. Dolasetron (Anzemet®) will not be available on the NIH formulary. (2) The guidelines promote single dose, oral prophylactic regimens for Chemotherapy-Induced Nausea & Vomiting (CINV). In addition, the guidelines promote a lower dose of intravenous ondansetron in single-dose regimens when a patient is unable to take an oral regimen. (3) For CINV prophylaxis, the guidelines employ a three level classification of emetic potential (High, Intermediate and Low). (4) The guidelines remove a previous recommendation for high dose regimens of 5-HT₃ antagonists in bone marrow transplant conditioning regimens. (5) The guidelines have been expanded to include other indications including prophylaxis for high-risk radiation therapy, prophylaxis for delayed CINV, prophylaxis and treatment of post-operative nausea and vomiting, and it provides treatment options for established nausea and vomiting. (6) A "grade of recommendation" was added to the drug and dosing regimen recommendations based on the strength of scientific evidence that support their use.

The complete antiemetic guidelines are provided below. Revisions to the MIS order screens for the 5-HT₃ antagonists will be occurring over the next few months. A pocket guide is also being produced as a reference source for prescribers and clinicians.

Updated NIH Clinical Center

Antiemetic Guidelines

The following drug regimens and dosing recommendations were assembled by the NIH Clinical Center Antiemetic Task Force in 2002. The selected antiemetic regimens were based on a review of primary medical literature, published national guidelines, internal expert opinion, and Clinical Center Pharmacy Department drug acquisition costs.

The drug regimen and dosing recommendations for antiemetic prophylaxis have been graded by the NIH Clinical Center Antiemetic Task Force (2002) according to the strength of scientific evidence that support their use. The dosing regimens are graded A, B, C, or D based on the following criteria:

- A** Strong research-based evidence (multiple large, randomized, controlled trials or meta-analyses of such trials),
- B** Moderate research-based evidence (evidence is obtained from at least one well-designed, randomized, clinical trial),
- C** Limited research-based evidence (formal clinical trials were of less rigorous design than the definitions described for grades A or B), and
- D** Panel interpretation of information that did not meet inclusion criteria as research-based evidence as described for A-C above.

A 5-HT₃ receptor antagonist (e.g., ondansetron) is frequently the agent of choice for multiple indications and provides significant clinical benefit. However, 5-HT₃ antagonists are expensive and should be prescribed appropriately to minimize the cost to the Clinical Center. When available clinical evidence demonstrates alternative prophylactic or treatment options are equivalent, the task force recommends consideration of the less expensive alternative.

5-HT₃ Antagonists are Generally Not Indicated for the Following Scenarios

- ❖ Prophylaxis of CINV when the chemotherapy regimen has a low emetic potential.
- ❖ Prophylaxis or treatment of nausea and vomiting not due to antineoplastic drugs. (Alternative antiemetics are encouraged as the initial prophylaxis or treatment)
- ❖ 5-HT₃ antagonists should generally not be considered as first line agents for the prophylaxis of delayed nausea and vomiting. Although ondansetron may have utility in the prophylaxis of delayed CINV, prophylactic regimens for delayed CINV that do NOT include a 5-HT₃ antagonist should be considered first due to equivalence in efficacy and reduced cost.
- ❖ Anticipatory nausea and vomiting
- ❖ "PRN" orders of 5-HT₃ antagonists
- ❖ Concurrent use of more than one 5-HT₃ antagonist for prophylaxis or treatment of nausea and vomiting

Adults

Chemotherapy-Induced Nausea and Vomiting (CINV)

Prophylaxis – High Emetic Risk (> 30% risk of emesis)

Ondansetron 24mg po x 1 given 30 min. prior to chemotherapy + Dexamethasone* 8-20mg po/IV x 1 given 30 min. prior to chemotherapy (when permitted)*

Grade of recommendation: A

OR if unable to take po:

Ondansetron 0.15mg/kg IV x 1 given 30 min prior to chemotherapy + Dexamethasone* 8-20mg IV x 1 given 30 min. prior to chemotherapy (when permitted)*

Grade of recommendation: A

*(Methylprednisolone 40-125mg IV x 1 given 30 min prior to chemotherapy may be used as an alternative to dexamethasone)

Note: For chemotherapy or biologic regimens where emetic agents are given multiple times within the same day, or with high dose chemotherapy regimens (e.g., pre-BMT regimens), or with continuous IV infusions of emetogenic chemotherapy, multiple dose ondansetron regimens are acceptable. Examples: Ondansetron 8mg po or 0.15mg/kg IV q12h to q8h. Corticosteroids should NOT be used for antiemetic prophylaxis or treatment for aldesleukin (interleukin-2)-containing regimens.

BMT Conditioning Regimen

(see above note on prescribing multiple antiemetic doses per day for highly emetic chemotherapy)

Ondansetron 8mg po or 0.15mg/kg IV q12 to q8h + Dexamethasone (when permitted) for duration of chemotherapy regimen and for up to 24 hours afterward)

Grade of recommendation: C

CINV Prophylaxis – Intermediate Emetic Risk (10-30%)

Dexamethasone 4-20mg po/IV x 1 dose 30 min prior to chemotherapy (when permitted)*

OR

Dopamine antagonist as a single agent x 1 dose pre-chemotherapy (Refer to Antiemetics for Treatment of Chemotherapy and Radiation Therapy table for examples of alternative agents and doses.)

Grade of recommendation: D

Note: A corticosteroid is the preferred agent for this category of emetic risk. However, other agents such as the dopamine antagonists are acceptable alternatives. Examples of agents that have dopamine antagonist properties include prochlorperazine, chlorpromazine, haloperidol, thiethylperazine, metoclopramide, perphenazine, and promethazine.

**Note:* Corticosteroids are not permitted in some research protocols.

High Risk Radiation Therapy Prophylaxis (e.g., TBI, hemi-body, abdominal RT)

Ondansetron 8mg po, 1-2 hours prior to radiation therapy and, if indicated, repeat doses q8h on the day of RT and, if indicated, up to 1-2 days post RT (alternatively, 8mg IV doses of ondansetron at the same schedule, may be substituted).

Grade of recommendation: B

Dexamethasone may be combined with ondansetron (when permitted)*

Grade of recommendation: D

Delayed CINV Prophylaxis (cisplatin regimens)

Note: Delayed CINV refers to nausea & vomiting of a delayed onset that is distinct from acute nausea & vomiting symptoms. Delayed CINV was initially described with cisplatin therapy and has been arbitrarily defined as nausea & vomiting occurring 24 hours or more after chemotherapy. The incidence of delayed vomiting following cisplatin is greatest for the 24 hour period from 48 to 72 hours after treatment and progressively declines in the successive 24 hour periods usually resolving 96 hours post chemotherapy. Although the onset of delayed emesis was initially defined at 24 hours post chemotherapy, more recent evidence suggests that referable symptoms may occur as early as 16 hours after cisplatin.

Prophylactic regimens for delayed emesis should be initiated post cisplatin chemotherapy (*Grade of recommendation: A*). These regimens may be started 16 hours (*Grade of recommendation: D*) to 24 hours (*Grade of recommendation: A*) after the cisplatin is given.

Metoclopramide 20-40mg po Q6H x 4 days plus

Dexamethasone 4-8mg po Q12h x 4 days

Grade of recommendation: A

OR

Ondansetron 8mg po Q12h x 4 days plus

Dexamethasone 4-8mg po Q12h x 4 days

Grade of recommendation: B

OR

Dexamethasone 8mg po Q12H x 4 days

Grade of recommendation: B

OR

Compazine Spansules (prochlorperazine SR) 15mg po Q12H x 4 days (or prochlorperazine 10mg po q8h to q6h) plus Dexamethasone 4-8mg po Q12H x 4 days

Grade of recommendation: D

Delayed CINV prophylaxis (non-cisplatin regimens)

Note: Delayed CINV (see definition above for cisplatin regimens) has been described in association with the following chemotherapy regimens, and thus, patients may benefit from antiemetic prophylaxis.

- ❖ Carboplatin $\geq 300\text{mg/m}^2$ (\pm other cytotoxic agents)
- ❖ Cyclophosphamide $\geq 600\text{mg/m}^2$
- ❖ Cyclophosphamide + other emetogenic chemotherapy agents
- ❖ Cyclophosphamide + doxorubicin (or other anthracycline combinations)
- ❖ Doxorubicin $\geq 50\text{mg/m}^2$

Prophylactic regimens for delayed emesis should be initiated post chemotherapy for some non-cisplatin chemotherapy regimens (see above list; *Grade of recommendation: B*). These regimens may be started 16 hours (*Grade of recommendation: D*) to 24 hours (*Grade of recommendation: B*) after the chemotherapy is given.

Dexamethasone 4-8mg po q12h x 1-4 days (when permitted)*

Grade of recommendation: B

OR any of the combination regimens listed above for cisplatin containing regimens

Grade of recommendation: C

OR if dexamethasone is not permitted:

Metoclopramide 20-40mg po Q6H x 1-4 days

Grade of recommendation: D

OR

Ondansetron 8mg po q12h x 1-4 days

Grade of recommendation: D

OR

Compazine Spansules (Prochlorperazine SR)

15mg po q12h x 1-4 days

(OR Prochlorperazine 10mg po q8h to q6h x 1-4 days)

Grade of recommendation: D

Post-operative Nausea and Vomiting Prophylaxis

Patients who are at high risk of vomiting based on patient specific factors, operative procedure, and/or anesthetic factors should receive antiemetic prophylaxis against post-operative nausea and vomiting.

Ondansetron 4mg IV 1 hour immediately before induction of anesthesia

Grade of recommendation: A

Post-operative Nausea and Vomiting Treatment

Note: The rescue agent selected should complement and not duplicate any prophylactic regimen (i.e., use an agent with a different mechanism of action).

Ondansetron 4mg IV/PO q12h to q8h

Grade of recommendation: A

OR

Promethazine 12.5mg – 25 mg IV/PO q4-6h

Grade of recommendation: C

OR

Prochlorperazine 10mg IV/PO q4-6h

Grade of recommendation: C

**Note:* Corticosteroids are not permitted in some research protocols.

OR

Metoclopramide 10 mg IV/PO q4-6h

Grade of recommendation: C

Treatment of Nausea and Vomiting (Chemotherapy or Radiation-induced and Other Etiologies)

The table below lists antiemetic agents that are available at the NIH CC for use in the treatment of nausea and vomiting. The information is organized by pharmacologic

class and is not listed in any order of preference. Agent selection should be based on the suspected etiology, the desired pharmacologic effect, patient-specific factors, and cost. All patients receiving chemotherapy should have antiemetics available on an as-needed basis for rescue for breakthrough nausea and vomiting. The rescue agent selected should complement and not duplicate the prophylactic regimen (i.e., utilize an agent with a different mechanism of action).

Antiemetics for Treatment of Chemotherapy and Radiation Therapy-induced Nausea and Vomiting

(This table does NOT include antiemetic regimens for prophylaxis of CINV or RINV.)

Pharmacologic Classes/Agents	Dosage Form	Adult Dosages, Routes and Schedules
Dopaminergic Antagonists: Phenothiazines		
Chlorpromazine (<i>Thorazine</i> ®, others)	Oral solution	25-50mg po q 4-6 h
	Tablets	25-50mg po q 4-6 h
	Injection	25-50mg IVPB/IM q 4-6 h*
Perphenazine (<i>Trilafon</i> ®)	Tablets	2-4 mg po q 8 h
Prochlorperazine (<i>Compazine</i> ®, others)	Tablets	5-20mg po q 4-6 h
	Sustained Release Capsules	15mg po q 8-12 h or 30mg po q 12 h
	Suppositories	25mg pr q 4-6 h
	Injection	5-20mg IVPB/IM q 4-6 h*
Promethazine (<i>Phenergan</i> ®)	Tablets	12.5-25mg po q 4-6 h
	Suppositories	12.5-25mg pr q 4-6 h
	Injection	12.5-25mg IV q 4-6 h†
	Tablets	10-20mg po q 4-6 h
Dopaminergic Antagonists: Butyrophenones		
Haloperidol (<i>Haldol</i> ®, others)	Tablets	1-4mg po q6h
	Injection	1-4mg IVPB/IM q6h*
Substituted Benzamide		
Metoclopramide (<i>Reglan</i> ®, others)	Tablets	20-40mg (or 0.5mg/kg) po q6h
	Injection	20-40mg (or 0.5mg/kg) IV q6h‡
Corticosteroids		
Dexamethasone	Tablets / oral solution	4-10mg po q6-12h
	Injection	4-10mg IV q6-12h
Methylprednisolone	Injection	20-125mg IV/IM q6h
Benzodiazepines§		
Alprazolam (<i>Xanax</i> ®)	Tablets	0.125-0.5mg po q8h
Lorazepam (<i>Ativan</i> ®)	Tablets	0.5-1mg po q6-12h
	Injection	0.5-1mg IV q6-12h
Cannabinoids		
Dronabinol (<i>Marinol</i> ®)	Capsules	2.5-10mg mg po q6h
Serotonin (5-HT₃) Antagonists		
Ondansetron (<i>Zofran</i> ®)	Tablets	8mg po q8-12h
	Injection	8mg IV q8-12h

* Rapid IV administration may induce hypotension. Administer by slow IV infusion (e.g., 30 min. or consult a pharmacist for rate recommendation).

† Promethazine injection is an irritant. Use caution with intravenous administration, particularly during administration into a peripheral vein. Dilution with IVPB administration may be considered to reduce irritation.

‡ Higher doses of metoclopramide have been utilized for the prophylaxis of CINV for highly emetic chemotherapy. Consult a clinical pharmacist if a high-dose metoclopramide regimen is indicated.

§ Benzodiazepines lack intrinsic antiemetic effects and should not be used as single agents against emetogenic chemotherapy.

|| 5-HT₃ antagonists should not be used as first line agents for the treatment of nausea and vomiting. 5-HT₃ antagonists should only be used to treat nausea and vomiting when other antiemetic agents have failed, when the patient has unacceptable side effects from other antiemetics, or when other antiemetics are contraindicated.

When combining multiple antiemetic agents for prophylaxis or treatment, it is rational to select agents of different pharmacologic classes and/or mechanisms of action.

5-HT₃ antagonists should only be used to treat nausea and vomiting when other antiemetic agents have failed, when a patient has unacceptable side effects from other antiemetics, or when other antiemetics are contraindicated. 5-HT₃ antagonists should not be used to rescue non-responders (i.e., treating breakthrough N/V) unless they previously did not receive a 5-HT₃ antagonist as prophylaxis. PRN dosing of 5-HT₃ antagonists is strongly discouraged. When treating nausea and vomiting with 5-HT₃ antagonists, prescribe for a limited duration and continually assess response carefully taking other factors into consideration in the evaluation of possible effectiveness.

Pediatrics

Grade of recommendation: C (Note: Due to the general lack of large, randomized, controlled clinical trials in the pediatric population, the NIH antiemetic task force have given a general grade of recommendation of C for all the suggested regimens listed below.)

Chemotherapy-induced Nausea and Vomiting (CINV)

Prophylaxis - High Emetic Risk (> 30% risk of emesis)

Ondansetron 4mg (children 4-12 years) or 8mg (children > 12years) po 30 min. before chemotherapy and 4 and 8hrs after chemotherapy + Dexamethasone 4-10mg/m² po/IV x 1 given 30 min. prior to chemotherapy (when permitted)*

OR

Ondansetron 0.15mg/kg IV 30 min. prior to chemotherapy and 4 and 8hrs after chemotherapy + Dexamethasone 4-10mg/m² po/IV x 1 given 30 min. prior to chemotherapy (when permitted)*

High Risk Radiation Therapy Prophylaxis

(e.g., TBI, hemi-body, abdominal RT)

Ondansetron 4mg (children 4-12 years) or 8mg (children > 12 years) po, OR 0.15mg/kg IV 1-2 hours prior to radiation therapy with repeat doses, if indicated, q8h on the day of RT and, if indicated, up to 1-2 days post RT. (with or without Dexamethasone, if permitted)*

*Note: Corticosteroids are not permitted in some research protocols.

Antiemetics for Treatment of Chemotherapy and Radiation Therapy-induced Nausea and Vomiting (Pediatrics)

(This table does NOT include antiemetic regimens for prophylaxis of CINV or RINV.)

Pharmacologic Classes/Agents	Dosage Form	Pediatric Dosages, Routes and Schedules
Dopaminergic Antagonists: Phenothiazines		
Prochlorperazine (Compazine®)	Tablets	5mg po bid to tid (older children to adolescents) 10mg po bid to tid (adolescents)
	Sustained Release Capsules	15mg po Q12H (adolescents)
	Injection	6mg/m ² /dose IVPB Q6-12H* OR 0.1-0.15 mg/kg/dose IVPB Q6-12H* 0.5 mg/kg IVPB q 4-6 h†
Promethazine (Phenergan®)	Injection	
Substituted Benzamide		
Metoclopramide (Reglan®, others)	Tablets	0.5 mg/kg (up to 20-30mg) po Q4-6H
	Injection	0.5mg/kg (up to 20-30mg) IV Q4-6H†
Corticosteroids		
Dexamethasone	Tablets / oral solution	4-10 mg/m ² po x 1-2 doses/day
	Injection	4-10 mg/m ² IV x 1-2 doses/day
Benzodiazepines§		
Lorazepam (Ativan®)	Injection	1.5 mg/m ² IV q6-12h (max dose 2mg)
Antihistamines		
Diphenhydramine (Benadryl®)	Injection	0.5-1 mg/kg mg IV q6h (max dose 50mg)

* Rapid IV administration may induce hypotension. Administer by slow IV infusion (e.g., 30 min. or consult a pharmacist for rate recommendation).

† Promethazine injection is an irritant. Use caution with intravenous administration, particularly during administration into a peripheral vein. Dilution with IVPB administration may be considered to reduce irritation.

‡ Higher doses of metoclopramide have been utilized for the prophylaxis of CINV for highly emetic chemotherapy. Consult a clinical pharmacist if a high-dose metoclopramide regimen is indicated.

§ Benzodiazepines lack intrinsic antiemetic effects and should not be used as single agents against emetogenic chemotherapy.

Post-operative Nausea and Vomiting Prophylaxis

Ondansetron 0.05 to 0.15 mg/kg IV (maximum 4 mg) immediately before induction of anesthesia

Treatment of Nausea and Vomiting

The table below lists antiemetic agents that are available at the NIH CC for use in the treatment of nausea and vomiting of multiple etiologies. The information is organized by pharmacologic class and is not listed in any order of preference. Selection of an individual agent should be based on the suspected etiology, the desired pharmacologic effect, patient specific factors, and cost. All patients receiving chemotherapy should have antiemetics available on an as-needed basis for rescue for breakthrough nausea and vomiting. The rescue agent selected should complement, not duplicate the prophylactic regimen (i.e. utilize an agent with a different mechanism of action).

When combining multiple antiemetic agents for prophylaxis or treatment, it is rational to select agents of different pharmacologic classes and/or mechanisms of action.

5-HT₃ antagonists should only be used to treat nausea and vomiting when other antiemetic agents have failed, when a patient has unacceptable side effects from other antiemetics, or when other antiemetics are contraindicated. 5-HT₃ antagonists should also not be used to rescue non-responders (i.e., treating breakthrough N/V) unless they previously did not receive a 5-HT₃ antagonist as prophylaxis. PRN dosing of 5-HT₃ antagonists is strongly discouraged. When treating nausea and vomiting with 5-HT₃ antagonists, prescribe for a limited duration and continually assess response carefully taking other factors into consideration in the evaluation of possible effectiveness.

FDA Safety Alerts

- ❖ You can access the latest safety information from the Food and Drug Administration website. To access “Dear Health Professional” letters, other safety notifications, and labeling changes related to drug safety, just point your browser to www.fda.gov and click on “MedWatch.” MedWatch is the FDA’s medical products reporting program.
- ❖ You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to fdalists@archie.fda.gov. In the message body enter: *subscribe medwatch* and your e-mail address.

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